THE REPORT OF THE PARTY OF THE

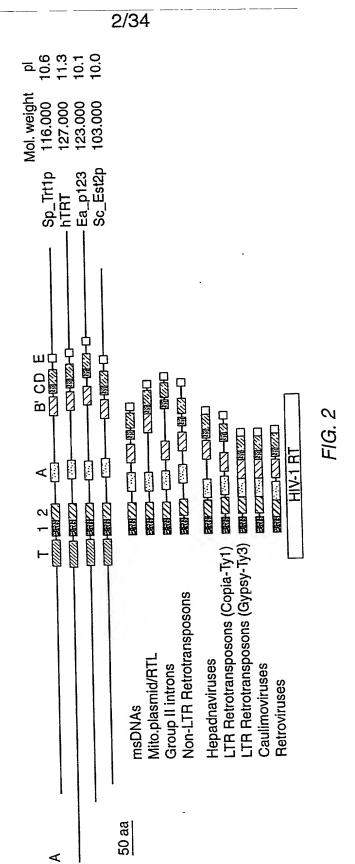
The first offer offer that the

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 1 of 34

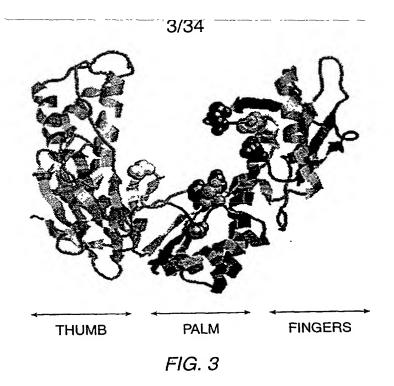
1/34

KORLLKKFINIVLPELYFWKFDVKSCYDSIPRMECMRILKD-ALKNENGFFVRSQYFFNTN EEFVCKWKQVGQPKLFFATMDIEKCYDSVNREKLSTFLKTTKLLSSDFWIMTAQILKRKN RIIAIPCRGADEEEFTIYKENHKNAIQPTQKILEYLRNKRPTSFTKIYSPTQIADRIKEF RPIMTFNKKIVNSDRKTTKLTTNTKLLNSHLMLKTLKN-RMFKDPFGFAVFNYDDVMKKY KKDLLKHRMFGR-KKYFVRIDIKSCYDRIKQDLMFRIVKK-KLKDPEFVIRKYATIHATS LKDFRWLFISD---IWFTKHNFENLNÕLAICFISWLFRQLIPKIIQTFFYCTEISSTVT-TREISWMQVET-SAKHFYYFDHEN-IYVLWKLLRWIFEDLVVSLIRCFFYVTEQQKSYSK TVYFRKDIWKLLCRPFI-TSMKMEAFEKINENNVRMDTQK-TTLPPAVIRLLPKK--NTF ISEIEWLVLGKRSNAKMCLSDFEKRKQIFAEFIYWLYNSFIIPILQSFFYITESSDLRNR IVYFRHDTWNKLITPFIVEYFKTYLVENNVCRNHNSYTLS--NFNHSKMRIIPKKSNNEF TYYYRKNIWDVIMKMSI-ADLKKETLAEVQEKEVEEWKKS-LGFAPGKLRLIPKK--TTF RLITN-LRKRFLIKMGSNKKMLVSTNQTLRPVASILKHLINEESSGIPFNLEVYMKLLTF **AKFLHWLMSVYVVELLRSFFYVTETTFQKNR** LFFYRKSVWSKLQSIGIRQHLKRVQLRDVSEAEVRQHREARPALLTSRLRFIPKP--DGL ** ** RPIVNMDYVVGARTFREKRAERLTSRVKALF-SVLNYERA Motif 3 (A) Motif 2 human human humar p123 EST2 EST2 p123 EST2 EST2 p123 p123 tez1 tez1 tez1 tez1

Atty. Docket No.: 015389-002630US
Applicant: Thomas R. Cech et al.
Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND
THERAPEUTIC METHODS
Sheet 2 of 34



Atty. Docket No.: 015389-002630US
Applicant: Thomas R. Cech et al.
Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND
THERAPEUTIC METHODS
Sheet 3 of 34



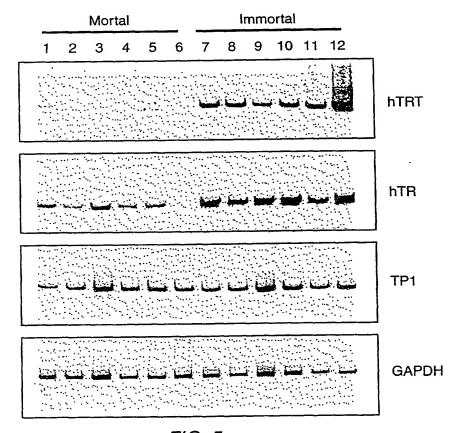


FIG. 5

Atty. Docket No.: 015389-002630US Applicant: Thomas R, Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 4 of 34

<u> </u>		4/04		
			181 197 179 146	
	82 87 100 68	20 25 7	S SSV LLL SSI SST	d H J J J
		SD	E W G PFGF WCGL WIGI	hlg Ifloy WMGI
	KLI MILI	E I I	MOUNT NOW	PARE NEW
	hhk IV K K VIAS FL K T	LAK LAK YTP	Motif E W G S KKRMPFFGFSV HGLFPWCGLLL QDYCDWIGISI KELEVWKHSST	hlg h ETPARFLØXNI ESKQSYLØVIL EPPFLWMØITL
	PRI PEV STF MRI	IKE FRK	MO 117 K 23 Q H 20 K	25 E E
	OLM SKL MEC	SGL		
	KQI PRI	TESHI WHI	YE FIN	THE CHANGE
	DE LOSA LOSA LOSA LOSA LOSA LOSA	DTI DRVI	I CE	TEED SDK
	F SCK	GY KCFD EAFD DAYF	STS VVV KFN KAN	Gh h ck GLTMNEEKT GISVNAAKT GLTTPDKKH
	Motif A hDh CY. IDIKSCY. VDVTGAY. MDIEKCY. FDVKSCY.	hDh SV <i>DL</i> K FL <i>D</i> IS 7L <i>D</i> VG	Motif D	E C C C C C C C C C C C C C C C C C C C
	M. C.	IEV IVL	MO FEK VPE SRE	NS- ADK LLR
	Motif A PCLYFh hDh CYD I RKKYFVRIDIKSCYDRI PELYFVKVDVTGAYDTI PKLFFATMDIEKCYDSV PELYFMKFDVKSCYDSI	NWF CSA KSV	Motif D h G c p N cK SLRGFEKHNFSTSLEK LVRGVPEYGCVVNLRK LINVSRENGFKFNMKK AMGGFQKYNAKANRDK	NFL SDW RQH
	Motif A PCLYFh hDh CYD I hhK K FGRKKYFVRIDIKSCYDRIKQDLMFRIVKKLKD PPPELYFVKVUVYGAYDTIPQDRLTEVIASIIKP GQPKLFFATMDIEKCYDSVNREKLSTFLKTTKLL VLPELYFMKFDVKSCYDSIPRMECMRILKDALKN AF	h hoh GY h FGGSNWFIEVDLKKCFOTISHDLIIKELKRYISD RKEYCSAVFLDISEAFDRVWHEGLLLKLAKILPY LKKKKSVTVLDVGDAYFSVPLDEDFRKYTAFTIP	NLS NTLS SYLL SKL	OLN KTF EEL
			Motif D A F h G c p N cK AKKFLNLSLRGFEKHNFSTSLEKTVI AKTFLRTLVRGVPEYGCVVNLRKTVV AVLFIEKLINVSRENGFKFNMKKLQT VINIKKLAMGGFQKYNAKANRDKILA	Gh h c k h KMIKRDLNNFLNS-LGLTMNEEKTLI NENYLKTFSDWADKWGISVNAAKTGH HRTKIEELRQHLLRWGLTTPDKKHQK
-	4444 0214	32 32 0	A AKI A KI V LI	NEI HR
	OTI SRV LLN IQF	DKF LFF	0000	7.40
10 8 8	STN RLT NTK KNA	TIF	Motif C LLRL DDFLhIT LLRLVDDFLFITVNKKD LLRLVDDFLLVTPHLTH LMRLTDDYLLITTQENN ILKLADDFLIISTDQQQ	r ddhh XVXYADDILIGVLGSKN LSTYADDILVLSSDILA IYQYMDDLYVGSDLEIG
X MKM HL K LK K	MLV RAE LTT ENH	ILD RLF QLG	T TVN TTC STL	VLG SSE SDI
CTSI CROI CAD	X NKK REK TTK IYK	MRM LLK WEV	LETI TILVII	hh IVI YVG
h	MGS) DRK EFT	DEV ERL ODF	C DDF DDF DDF DDF DDF	DDD TOOL
H W C	LIKI GAR' VNSI DEEI	KART KRI	Motif C LLRL DDFLhIT LLRLVDDFLFIT LRLVDDFLLVT LMRLTDDYLLIT ILKLADDFLIIS	F DDhhh RYADDILI TYADDILV QYMDDLYV
W L h I IWKLLCRPFI VWSKLQSIGI IWDVIMKMSI TWNKLITPFI	h CRFI CVVC CKIV GGAI	PRDI SLSI	I E E E E E	
MOCIFT WL hh hh pffy TE p p Y RK W L h I K WLYNSFIIPILQSFFYITESSDLRNRTVYFRKDIWKLLCRPFITSMKM WLMSVYVVELLRSFFYVTETTFQKNRLFFYRKSVWSKLQSIGIRQHLK WIFEDLVVSLIRCFFYVTEQQKSYSKTYYYRKNIWDVIMKMSIADLKK WLFRQLIPKIIQTFFYCTEISSTVT-IVYFRHDTWNKLITPFIVEYFR	OCIF 2 FRAL h h K FRLITULRKRFLIKMGSNKKMLVSTNQTL LRPIVNMDYVVGARTFRREKRAERLTSRV FRPIMTFNKKIVNSDRKTTKLTTNTKLLN RRIIAIPCRGADEEFFTIYKENHKNAIQP R	hr h Irpisvgnprdkivqevmrmildtifdkk Yrpislisglskmferlilkrifrvdlfk Wrkivdfrelnkrtqdfwevqlgiphpag	6 7 8 8	55 7 4
Y RK YFRKD: 'FYRKS' 'YYRKN: 'YFRHD'	OCIF 2 FRNI h FRLITNL LRPIVNM FRPIMTF	h PLSY PISI KLVI	P SPT SPT SPL SPL	OY I YHP KQN
RETA REF KTY	Motif FRhI FRLIT LRPIV FRPIM	hR h IRPLS YRPIS WRKLV	ZYLS CLF7 SSLC ?YS]	VLEI PHI PFKI
P LLRNH QKNH SYSP	0001	0.04	LEEN	/DNM (PEL)
D SSE TITE OOK	DGTT	KG GKS DST	DE GOM	TTLY SSD STTX
	PKK	K K K	h y in y i	h IIVMT SIFSS SSMT
Motif Defy SffyII CffyUI TffyUI	if 1 hrhipkk Trlipkk Lrfipkp Lrlipkk	h h VNI KMI	L S I VI	HACE
MOCLIF T WL hh hh pffy TE WLYNSFIIPILQSFFYITES WLMSVYVVELLRSFFYVTET WLFEDLVVSLIRCFFYVTEQ WLFRQLIPKIIQTFFYCTEI	Motif 1 hRhI PAVIRLL TSRLRFI PGKLRLI HSKMRII	p hh h K MKIVNIPKI IAQVKMILKI ITPVFAIKKI	B' SSF STL SST SAP	pP hh ISPILCN IGPILYS ISPAIFQ
n h IPI VEL VSL	M h rlpp stap	FKP WKH PYN	SILL SILL SILL SILL SILL	SLISNE
h SFI VV OLV	KTT RPA SLG	KFK PDA PEN	Motif B' Pogs Ls Pogsiles Pogsiles Pogsiles	hpog Lpogs Vpogs Vpogs
YNY IMS IFEI	OTQI REAL WKK	STG	SG G G C C C C C C C C C C C C C C C C C	LGL PGC NVL
WILL WILL	Motif 1 halipkk p hnuvrmdtokttleprauirllerknt- EURQHREARPALLTSRLRFIPKPDG- KEVEEWKKSLGFAPGKIRLIPKKTT- CRNHNSYTLSNFNHSKMRIIPKKSNN	p hh h K LSNELGTGKFKFKPMRIVNIPKPKGG SILRIGYYPDAWKHAQVKMILKPGKS EGKISKIGPENPYNTPVFAIKKKDST	NO VO	KPM ZIG Y Q Y
429 546 366	NNV EVI CRN	LSI SII	Motif B' K Y Q GIPQGS LS hL h Y DL SQYLQKVGIPQGSILSSFLCHFYMEDLIDEYLSFT KSYVQCQGIPQGSILSTLLCSLCYGDMENKLFAGI KFYKQTKGIPQGLCVSSILSSFYYATLEESSLGFL KCYIREDGLFQGSLSAPIVDLVYDDLLEFYSEFK	hPQG pP hh h TYHKPMLGLPQGSLISPILCNIVMTLVDNWLEDYI RAGQIGAGVPQGSNLGPILYSIFSSDMPLPHIYHP GIRYQYNVLPQGWKGSPAIFQSSMTKILEPFKKQN
d	(1) Eg	Eu	Ω. Ω.	
COLL TTTT	COT Frt1 122 122 122	20n 14.	CON Trt. P12	20n 1811 11818
TRT con Sp_Trtlp hTRT Ea_p123	TRT con Sp_Trtlp hTRT Ea_p123 Sc_Est2p	RT con Sc_a1 Dm_TART HIV-1	TRT con Sp_Trt1p hTRT Ea_p123 Sc_Est2p	RT con Sc_a1 Dm_TART HIV-1
C에컨Ħ데	C. 01 M M M	- ** FI FI	C: 34 pm pm 44	

Atty. Docket No.: 015389-002630US
Applicant: Thomas R. Cech et al.
Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND
THERAPEUTIC METHODS
Sheet 5 of 34

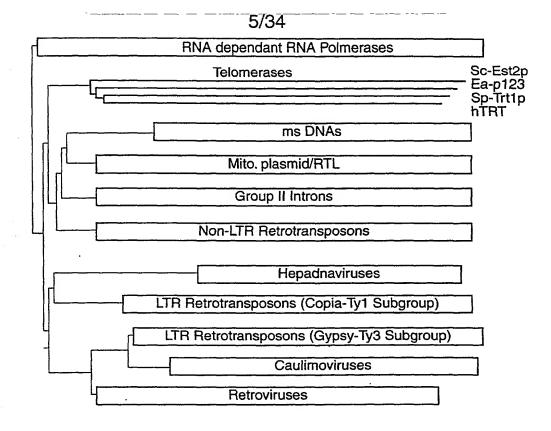


FIG. 6

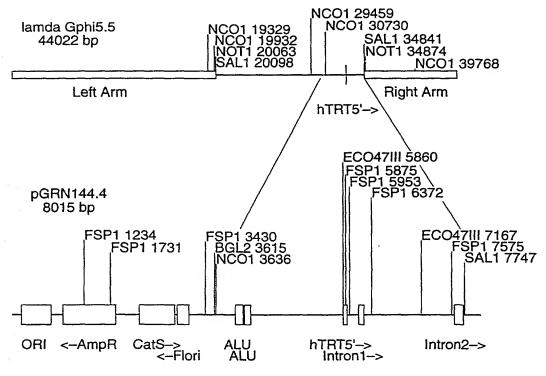


FIG. 7

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 6 of 34

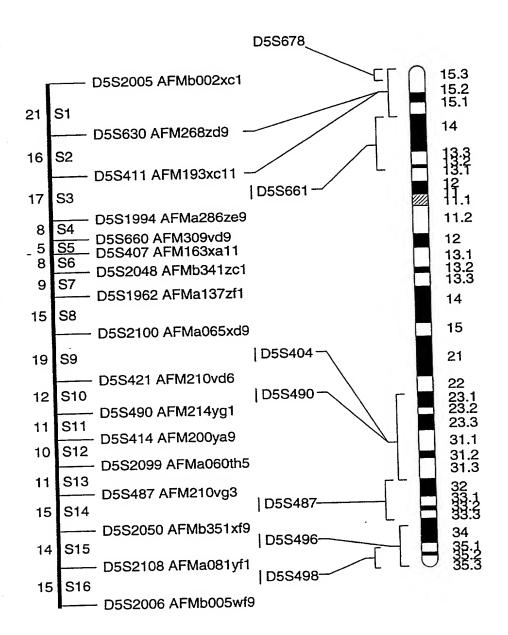


FIG. 8

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 7 of 34

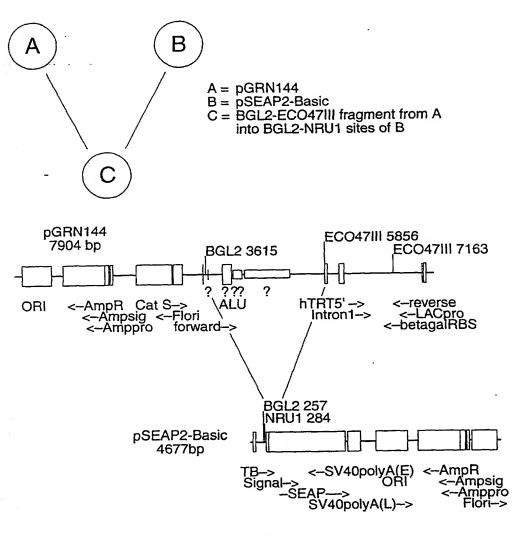


FIG. 9

Atty. Docket No.: 015389-002630US
Applicant: Thomas R. Cech et al.
Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND
THERAPEUTIC METHODS
Sheet 8 of 34

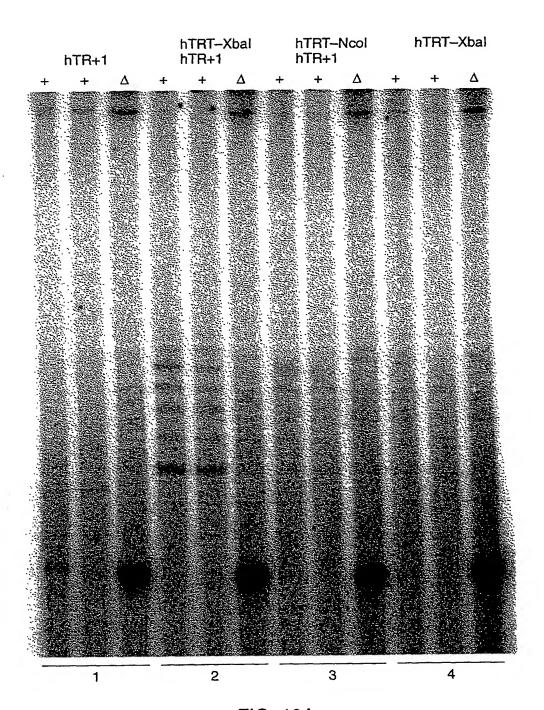


FIG. 10A

Atty. Docket No.: 015389-002630US
Applicant: Thomas R. Cech et al.
Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND
THERAPEUTIC METHODS
Sheet 9 of 34

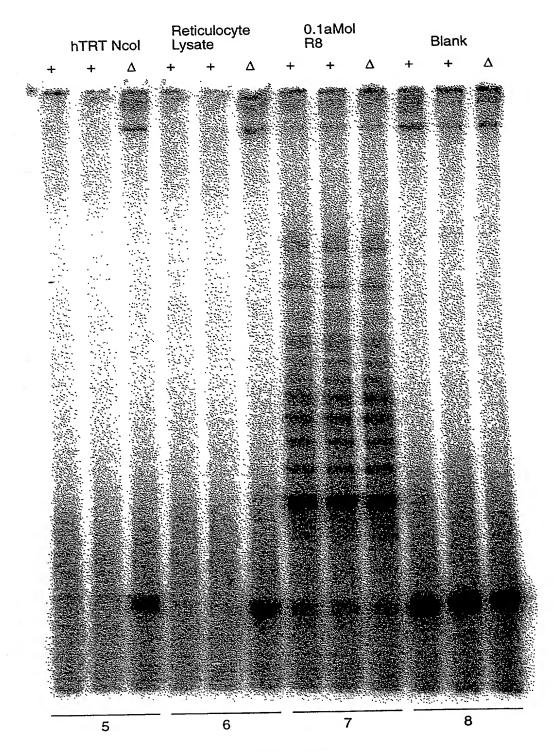


FIG. 10B

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 10 of 34

. Telomerase Specific Motifs

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS

Sheet 11 of 34

> NFkB_CS1 GGGRQTYYQC NFkB-MHC-I.2 TGGGCTTCCCC

Intron1

301 GCTGGGGTTGAGGGCGGCGGGGGGAACCAGCGACATGCGGAGAGCAGCGCAGCGACTCCGACCCCAACTCCCGCCGGCCCCCTTGGTCGCTGTACGCCTCTCGTCGCGCGCCCCTGAG

NFkB_CS1 GGGRQTYYQC NFkB_CS2 RGGGRMTYYCC

ĻĎ

ļ.

l die

TÜ

Topo_II_cleavage_site RNYNNCNNGYNGKTNYNY

361 AGGGCGCTTCCCCCGCAGGTGTCCTGCCTGAAGGAGCTGGTGGCCCGAGTGCTGCAGAGG TCCCGCGAAGGGGGCGTCCACAGGACGGACTTCCTCGACCACCGGGCTCACGACGTCTCC

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 12 of 34

AAAACCCCAA AACCCCAAAA CCCCTTTTAG AGCCCTGCAG TTGGAAATAT AACCTCAGTA TTAATAAGCT CAGATTTTAA ATATTAATTA CAAAACCTAA 51 ATGGAGGTTG ATGTTGATAA TCAAGCTGAT AATCATGGCA TTCACTCAGC 101 TCTTAAGACT TGTGAAGAAA TTAAAGAAGC TAAAACGTTG TACTCTTGGA 151 TCCAGAAAGT TATTAGATGA AGAAATCAAT CTCAAAGTCA TTATAAAGAT 201 TTAGAAGATA TTAAAATATT TGCGCAGACA AATATTGTTG CTACTCCACG 251 AGACTATAAT GAAGAAGATT TTAAAGTTAT TGCAAGAAAA GAAGTATTTT 301 CAACTGGACT AATGATCGAA CTTATTGACA AATGCTTAGT TGAACTTCTT 351 TCATCAAGCG ATGTTTCAGA TAGACAAAAA CTTCAATGAT TTGGATTTCA 401 ACTTAAGGGA AATCAATTAG CAAAGACCCA TTTATTAACA GCTCTTTCAA 451 CTCAAAAGCA GTATTTCTTT CAAGACGAAT GGAACCAAGT TAGAGCAATG 501 ATTGGAAATG AGCTCTTCCG ACATCTCTAC ACTAAATATT TAATATTCCA 551 GCGAACTTCT GAAGGAACTC TTGTTCAATT TTGCGGGAAT AACGTTTTTG 601 ATCATTTGAA AGTCAACGAT AAGTTTGACA AAAAGCAAAA AGGTGGAGCA 651 GCAGACATGA ATGAACCTCG ATGTTGATCA ACCTGCAAAT ACAATGTCAA 701 GAATGAGAAA GATCACTTTC TCAACAACAT CAACGTGCCG AATTGGAATA 751 ATATGAAATC AAGAACCAGA ATATTTTATT GCACTCATTT TAATAGAAAT 801 AACCAATTCT TCAAAAAGCA TGAGTTTGTG AGTAACAAAA ACAATATTTC 851 AGCGATGGAC AGAGCTCAGA CGATATTCAC GAATATATTC AGATTTAATA 901 GAATTAGAAA GAAGCTAAAA GATAAGGTTA TCGAAAAAAT TGCCTACATG 951 CTTGAGAAAG TCAAAGATTT TAACTTCAAC TACTATTTAA CAAAATCTTG 1001 TCCTCTTCCA GAAAATTGGC GGGAACGGAA ACAAAAAATC GAAAACTTGA 1051 TAAATAAAAC TAGAGAAGAA AAGTCGAAGT ACTATGAAGA GCTGTTTAGC 1101 TACACAACTG ATAATAAATG CGTCACACAA TTTATTAATG AATTTTTCTA 1151 CAATATACTC CCCAAAGACT TTTTGACTGG AAGAAACCGT AAGAATTTTC 1201 AAAAGAAAGT TAAGAAATAT GTGGAACTAA ACAAGCATGA ACTCATTCAC 1251 AAAAACTTAT TGCTTGAGAA GATCAATACA AGAGAAATAT CATGGATGCA 1301 GGTTGAGACC TCTGCAAAGC ATTTTTATTA TTTTGATCAC GAAAACATCT 1351 ACGTCTTATG GAAATTGCTC CGATGGATAT TCGAGGATCT CGTCGTCTCG 1401 CTGATTAGAT GATTTTCTA TGTCACCGAG CAACAGAAAA GTTACTCCAA 1451 AACCTATTAC TACAGAAAGA ATATTTGGGA CGTCATTATG AAAATGTCAA 1501 TCGCAGACTT AAAGAAGGAA ACGCTTGCTG AGGTCCAAGA AAAAGAGGTT 1551 GAAGAATGGA AAAAGTCGCT TGGATTTGCA CCTGGAAAAC TCAGACTAAT 1601 ACCGAAGAAA ACTACTTTCC GTCCAATTAT GACTTTCAAT AAGAAGATTG 1651 TAAATTCAGA CCGGAAGACT ACAAAATTAA CTACAAATAC GAAGTTATTG 1701 AACTCTCACT TAATGCTTAA GACATTGAAG AATAGAATGT TTAAAGATCC 1751 TTTTGGATTC GCTGTTTTTA ACTATGATGA TGTAATGAAA AAGTATGAGG 1801 AGTTTGTTTG CAAATGGAAG CAAGTTGGAC AACCAAAACT CTTCTTTGCA 1851 ACTATGGATA TCGAAAAGTG ATATGATAGT GTAAACAGAG AAAAACTATC 1901 AACATTCCTA AAAACTACTA AATTACTTTC TTCAGATTTC TGGATTATGA 1951 CTGCACAAAT TCTAAAGAGA AAGAATAACA TAGTTATCGA TTCGAAAAAC 2001 TTTAGAAAGA AAGAAATGAA AGATTATTTT AGACAGAAAT TCCAGAAGAT 2051 TGCACTTGAA GGAGGACAAT ATCCAACCTT ATTCAGTGTT CTTGAAAATG 2101 2151 AGAAATTATT TTAAGAAAGA TAACTTACTT CAACCAGTCA TTAATATTTG 2201 CCAATATAAT TACATTAACT TTAATGGGAA GTTTTATAAA CAAACAAAAG 2251 GAATTCCTCA AGGTCTTTGA GTTTCATCAA TTTTGTCATC ATTTTATTAT 2301 GCAACATTAG AGGAAAGCTC CTTAGGATTC CTTAGAGATG AATCAATGAA 2351

FIG. 13

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 13 of 34

2401	CCCTGAAAAT	CCAAATGTTA	ATCTTCTAAT	GAGACTTACA	GATGACTATC
2451	TTTTGATTAC	AACTCAAGAG	AATAATGCAG	TATTGTTTAT	TGAGAAACTT
2501	ATAAACGTAA	GTCGTGAAAA	TGGATTTAAA	TTCAATATGA	AGAAACTACA
2551	GACTAGTTTT	CCATTAAGTC	CAAGCAAATT	TGCAAAATAC	GGAATGGATA
2601	GTGTTGAGGA	GCAAAATATT	GTTCAAGATT	ACTGCGATTG	GATTGGCATC
2651	TCAATTGATA	TGAAAACTCT	TGCTTTAATG	CCAAATATTA	ACTTGAGAAT
2701	AGAAGGAATT	CTGTGTACAC	TCAATCTAAA	CATGCAAACA	AAGAAAGCAT
2751	CAATGTGGCT	CAAGAAGAAA	CTAAAGTCGT	TTTTAATGAA	TAACATTACC
2801	CATTATTTTA	GAAAGACGAT	TACAACCGAA	GACTTTGCGA	ATAAAACTCT
2851	CAACAAGTTA	TTTATATCAG	GCGGTTACAA	ATACATGCAA	TGAGCCAAAG
2901	AATACAAGGA	CCACTTTAAG	AAGAACTTAG	CTATGAGCAG	TATGATCGAC
2951	TTAGAGGTAT	CTAAAATTAT	ATACTCTGTA	ACCAGAGCAT	TCTTTAAATA
3001	CCTTGTGTGC	AATATTAAGG	ATACAATTTT	TGGAGAGGAG	CATTATCCAG
3051	ACTTTTTCCT	TAGCACACTG	AAGCACTTTA	TTGAAATATT	CAGCACAAAA
3101	AAGTACATTT	TCAACAGAGT	TTGCATGATC	CTCAAGGCAA	AAGAAGCAAA
3151	GCTAAAAAGT	GACCAATGTC	AATCTCTAAT	TCAATATGAT	GCATAGTCGA
3201	CTATTCTAAC	TTATTTTGGA	AAGTTAATTT	TCAATTTTTG	TCTTATATAC
3251_	TGGGGTTTTG	GGGTTTTGGG	GTTTTGGGG		

FIG. 13 (CONTINUED)

```
MEVDVDNQAD NHGIHSALKT CEEIKEAKTL YSWIOKVIRC RNOSOSHYKD
     LEDIKIFAQT NIVATPRDYN EEDFKVIARK EVFSTGLMIE LIDKCLVELL
 51
101
      SSSDVSDRQK LQCFGFQLKG NQLAKTHLLT ALSTQKQYFF QDEWNQVRAM
      IGNELFRHLY TKYLIFQRTS EGTLVQFCGN NVFDHLKVND KFDKKQKGGA
151
201
     ADMNEPRCCS TCKYNVKNEK DHFLNNINVP NWNNMKSRTR IFYCTHFNRN
     NQFFKKHEFV SNKNNISAMD RAQTIFTNIF RFNRIRKKLK DKVIEKIAYM
251
301
     LEKVKDFNFN YYLTKSCPLP ENWRERKQKI ENLINKTREE KSKYYEELFS
     YTTDNKCVTQ FINEFFYNIL PKDFLTGRNR KNFQKKVKKY VELNKHELIH
351
     KNLLLEKINT REISWMQVET SAKHFYYFDH ENIYVLWKLL RWIFEDLVVS
401
     LIRCFFYVTE QQKSYSKTYY YRKNIWDVIM KMSIADLKKE TLAEVQEKEV
451
501
     EEWKKSLGFA PGKLRLIPKK TTFRPIMTFN KKIVNSDRKT TKLTTNTKLL
     NSHLMLKTLK NRMFKDPFGF AVFNYDDVMK KYEEFVCKWK QVGQPKLFFA
551
601
     TMDIEKCYDS VNREKLSTFL KTTKLLSSDF WIMTAQILKR KNNIVIDSKN
651
     FRKKEMKDYF ROKFOKIALE GGOYPTLFSV LENEONDLNA KKTLIVEAKO
701
     RNYFKKDNLL QPVINICQYN YINFNGKFYK QTKGIPQGLC VSSILSSFYY
751
     ATLEESSLGF LRDESMNPEN PNVNLLMRLT DDYLLITTQE NNAVLFIEKL
801
     INVSRENGFK FNMKKLQTSF PLSPSKFAKY GMDSVEEQNI VQDYCDWIGI
851
      SIDMKTLALM PNINLRIEGI LCTLNLNMQT KKASMWLKKK LKSFLMNNIT
901
     HYFRKTITTE DFANKTLNKL FISGGYKYMQ CAKEYKDHFK KNLAMSSMID
     LEVSKIIYSV TRAFFKYLVC NIKDTIFGEE HYPDFFLSTL KHFIEIFSTK
951
1001
     KYIFNRVCMI LKAKEAKLKS DOCOSLIQYD A
```

FIG. 14

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 14 of 34

80 1160 2240 2370 240 2580 2880 3880	1018 20	1078 40	1138 60	1198 80	1272 86	1332 106	1405 113	1469 128
ggtaccgatttactttcctttcttcataagctaattgcttcctcgaacgctcctaaatctctggaaatatttttacaagga 80 acteaataacaataacaataccaagtcaattgaaggtgttattagtgatcgataatatttctattttattgtgtgttattagtgatcgataatatttctattttattgtgtgttattagtgatcgataatatttcggtcgtta 160 ccaagtataaaggacaaaagaacaacttccttcccccctaaagacttttaattttattta	PAT GTA	1019 TAC CTA TGT ACC TTA AAT GAT TAT GTA CAA CTT GTT TTG AGA GGG TCG CCG GCA AGC TCG 1078 $21~\rm Y$ L C T L N D Y V Q L V L R G S P A S S 40	PP CTT	CCT CCA	1199 AAA TGC TCA CAG TCA GAG gtatatattttgttttgatttttttttttctattcgggatagctaatatgggcag 1272 $81~{ m K}$ C S Q S E	1273 CTA ATA GCG AAT GTT GAA CAG ATG TTC GAT GAA AGT TTT GAG CGT CGA AGG AAT CTA 1332 87 L I A N V V K Q M F D E S F E R R N L 106	gaga	ttgtatttaaccgataaag AAT CAT GAA GAT TTT CGA GCC ATG CAT GTA AAC GGA GTA CAA AAT 1469 N H E D F R A M H V N G V Q N 128
acttt gatacac tttta cctta cctta ccaaaa tcatc tagtt tagtt	CAC H	ACC T	ATA I	GTA V	cAG Q	AAT N	999 9	cgata
tact sagara sagara sagara cattr cattr sattra saaaa	AA CA H	ST AC	AT AT I	or Gr	SA CA	SG AA	4A GG G	accga
cgar tragact tragact tragact tragact tragact tragact tragact tragact tragact	00 B	F. P. T.	SC A	CG A	3C T(ra g	rg A	tta
tagacharacharacharacharacharacharacharach	lG A	S D II	AT A(AT TK	₹ ĭ	Æ H	S A M	gtal
	9 AT 1 M	9 TP	9 TP	9 CP	9 A.	3 CT 7 L	3 CI	6 tt
1 8 1 1 6 1 1 6 1 1 6 1 1 6 1 1 6 1 1 6 1 1 6 1 1 6 1 1 6 1 1 6 1 6 1 1 6	95	101	107	113	119 8	127 8	1333	1406 114

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 15 of 34

1529 148	1601 155	1661 175	1721 195	1781 215	1841 235	1907 245	1967 265	2027 285	2087 305	2147 325	2207 345	2267 365
caa o	3 3 9	GAC D	GTG V	AAA K	TAT Y	ų	AGG R	GTA V	ACA T	ATT I	GCG A	ATA I
TGG W	ATC I	AAT	ACT T	CGC R	TCC	TTT AAC F N	CCA P	CTG L	CAA Q	TAT Y	TTT F	AGG R
AAT	ag T	CCA P	GAA E	GCC A	TCA S	TAT TT Y F	TTT F	CCA P	GAA E	CCA P	GTG V	CAA
AAA K	gtat	CTT L	GAG E	AGC S	AGG R	CTA TZ L Y	ATT I	ATT I	ATT I	TGC	CAG Q	AAC
TCA S	gtaaataccggttaagatgttgcgcactttgaacaagactgacaagtatag T $^{ m ATC}$	GCT A	\mathbf{r}	AAA K	TAC Y	AT C	TGG W	GTG V	TTA	TAT	AAC N	GGT G
GAG E	yactç	GAG E	GTG V	AAT N	$ ext{TTT}$	G gtaactaatactgttatccttcataactaattttag AT D	CAA Q	AAA K	CCT P	CAT	F CCG	TGG W
$_{\rm L}^{\rm CTT}$	ıcaaç	TTT F	AAT N	CAA Q	ATT I	att	$_{\rm L}^{\rm CTT}$	CAC H	TAC	AAC	AAG K	ATC I
ATA I	tgaa	ATT I	AAT N	ACT T	AGC S	actai	TGG W	TTG L	GTA V	TAC Y	TTA L	TTA
TCT	actt	AGT	AAA K	ATT I	TTT F	zata	ATG M	CAA O	AAG K	GTT V	TCC	AAA K
ATA I	gege	GGA G	$ ext{TTT}$	TCC	AGG R	sctto	CAC	AAG K	CTA L	AAA K	TAT Y	CCT
CTT	tgtt	AAA K	$_{\rm L}^{\rm CTT}$	ACA T	AGT S	tato	GTA V	GTG V	CTC L	TCA	AGT S	TTT F
TAC	aaga	TCC S	CCA P	GAA E	ATT I	actgl	ACA	CAA Q	CGT R	CTA L	CTT L	GTG
AAT N	ggtt	TTA L	ATA I	ATT I	TCA	taati	AAC	TTT F	AAA K	TCT	ATC	CGA R
CCT P	tacc	TTA L	၁၅၅ ၁၅၅	ACC T	ATT I	taact	CGG R	GCA A	CCC	ATT I	AAA	GTT V
TTT. F	ıtaaa	TAC Y	TCT S	CGA R	AGC S		GAT D	AAC N	GTG V	CGT R	GAA	CTT
ACT	AT	CAT H	ATT I	AAG K	AAT N	CAA O	${ m TGT}$	ATA I	GTT V	CAT H	GAT D	ATT
TCT	GAA E	ATG M	CAG Q	AGA R	TGG W	AAG K	ATT I	CTT	ACA T	CTC	GAT D	TCC
GTT V	TTA L	GCC A	CTT	AAA K	TCC	TTT F	TCT		AGT S	CGA R	CAC H	CGA R
5. 2.1.	TTG	GAT D	TAC Y	AAA K	GTT V		CAC H		CAG Q			$_{\rm L}^{\rm CTT}$
GAT D	$^{ m CTT}$	AGT S	AAT N	TCA S	GAA E							$_{\rm F}^{\rm TT}$
1470			1662 176	1722 196	1782	1842	1908 246	1968 266	2028	2088 306	2148	2208 346

FIG. 15 (CONTINUED)

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 16 of 34

2336 375	2396 395	2465 405	2525 425	2585 445	2645 465	2705 485	2775 495	2835 515	2906 524	2967 542	3027 562	3088 581	
ACT T	AAG K	GGA G	GCG A	TAT Y	AAA K	GAG E	taaagtattttttgcaaaagctaatttcag AAC AAT GTT AGG ATG GAT ACT CAG AAA ACT N N V R M D T Q K T	ACG T	gtattaattttggtcatcaatgtactttacttctaatctatta	GTG V	GAG E	gtaat	
GAA	ATA I	CTT L	TTT F	TTT F	TGG W	AAC N	S X X	ATT	aatc	CCI	${ m TTG}$	ອ ອ	
CTC D	AAC	GTC V	ATA I	TTT F	ATT I	ATA I	CA	CTC	ttct	CGA R	AAC N	TTT F	
g AC	AGT S	CTA L	CAA O	TCT	GAT D	AAA K	A AC	CGT R	tac	TTA L	TTT F	ATG M	
асса	ATG	TGG W	AAG K	CAA	AAA K	GAA E	GA7	TTT F	actt	ACT T	CCA P	CGA R	
ttt	TTA L	GAA	CGC	TTA L	AGA R	TTT F	ATG M	ACC	ıatgt	CAA ACT TTA CGA CCT Q T L R P	GGT ATT CCA TTT AAC G I P F N	CAC H	
G gtattgtataaaatttattaccactaacgattttaccag AC D	rAT Y	ATT	AAA K	ATT TTA I L	GTT TAT TTT AGA V Y F R	AAA ATG GAA GCG TTT GAA AAA ATA AAC K M E A F E K I N	AGG R	GCA GTT ATT CGT CTA TTA CCT AAG AAG AAT ACC TTT CGT CTC ATT A V I R L L P K K N T F R L I	atce	AAC	GGT G	CTT AAG	
acta	CAT TAT H Y	GAA	GAG	CCT	TAT Y	GAA E	GTT V	AAG K	ggto	ACG	AGT	CTT	<u>~</u>
tacci	TTA (TCA	TTT F	ATA I	GTT V	ATG M	N N	AAG K	ttt	AGT S	AGT S	CTT L	15 IUED
ctati	AGT S	ATT I	GAT D	ATA I	CGA ACT (AAA K	AAC	CCT P	taat	AAA ATG TTA GTC AGT K M L V S	GAA AGT I	ACT TTT AAG AAG GAT T F K K D	FIG. 15 (CONTINUED)
aaati	rrr F	gccaaatttttttaccattaattaacaatcag ATT I	AGT S	TTT	CGA R	ATG M	tcag	TTA L	gtat	TTA L	gaa e	AAG K	00
tata	GAG TCT S	caat	TTA	TCG S	AAT N	CCC TTT ATT ACA TCA ATG P F I T S M	attt	$_{\rm L}^{\rm CTA}$	TTA ATA AAG L I K	ATG M	AAT N	AAG K	
attg	GAG	ttaa	TGC	AAT N	CGA R	ACA T	taat	CGT R	ATA I	AAA. K	ATC I	TTT F	
G gt	AGA TAC (R	ttaa	ATG M	TAC Y	TTA L	ATT I	ıaago	ATT I	TTA L	AAA K	TTA L	ACT T	
AAA K	AGA R	acca	AAA K	$_{\rm L}^{\rm cTA}$	GAT D	TTT F	ıcaaa	GTT V	$ ext{TTC}$	AAC N	CAT H	CTT	
TTA	TCG	ttt	GCG	TGG W	AGT S	CCC	ttt	GCA A	AGA R	TCA S	AAA K	$_{\rm L}^{\rm CTT}$	
ATA I	TTA L	attt	AAT N	TAC Y	TCA S	CGA	attt	rg cct cca	AAA K	GGT G	CTG L	AAG K	
ATA	AAA	ccaa	TCA	ATC I	GAA E	JGC C	ıaagt	CCT	AGA R	ATG M	ATA I	ATG M	
GAG	TTG	ע	AGG R	TC	ACT	TTG	ttta	${ m TTG}_{ m L}$		ttagcag	TCG S	TAC	
TTT (F	TTC	gtaata	AAA	¥.	ATC	crc	gtattt	ACT		tag	GCA	GTT V	
366 1					2586 446	2646 466	2706	2776	2836 516	2907	2968 543	3028 563	

17/34

3155 591	3215 611	3275 631	3343 643	3405 659	3465 679	3532 692	3593 708	3653 728	3713 748	3777 764	3840 778	3900 798
3089 tatataatgogogattootoattattaattttgoag G CGT AAG AAG TAT TTT GTA CGG ATA GAT ATA R K Y F V R I D I 582	AAA TCC TGT TAT GAT CGA ATA AAG CAA GAT TTG ATG TTT CGG ATT GTT AAA AAG AAA CTC K S C Y D R I K Q D L M F R I V K K L	AAG GAT CCC GAA TTT GTA ATT CGA AAG TAT GCA ACC ATA CAT GCA ACA AGT GAC CGA GCT K D P E F V I R K Y A T I H A T S D R A	ACA AAA AAC TTT GTT AGT GAG GCG TTT TCC TAT T gtaagtttatttttttggaattttttaacaa T K N F V S E A F S Y F	3344 attetttttag TT GAT ATG GTG CCT TTT GAA AAA GTC GTG CAG TTA CTT TCT ATG AAA ACA 644		AAA ATG CTC K M L	ctaatgaaactag A ^ŋ	ATT CTG TCA TCT TTT TT T L S S F L	TTT ACG AAA AAG AAA GGA F T K K K G	GTT AAT AAA V N K	taagttct	3841 ATA AAC TTT GAA AAT AGT AAT GGG ATA ATA AAC AAT ACT TTT TTT AAT GAA AGC AAG AAA 779 I N F E N S N G I I N N T F F N E S K K
<u> </u>	ິຕິ	ຸຕິ	ć.	c	М	c	m	(1)	(*)	(*1	* · ·	• •

The first first that the second section of the section of the second section of the section of the second section of the second section of the second section of the second section of the secti

(CONTINUED)

and the state of t

3960 818	4020 838	4089 848	4149 868	4209 888	4274 903	4339 917	4401 935	4468 946	4528 966	4588 986	4665 989
TGT	999 9	gtatactgtgtaactgaataatagctgacaaataatcag A TCG S	TCT	AAA K	ACG G gtgagtacttatttaactaga $_{ m T}$ D	3 GCC	ytgtc	acacatcag G CTT TTT TGT CTT GGA ATG AGA GAT GGT TTG AAA L F C L G M R D G L K	ACT	ATA I	tgtcattttcaatttattatatacatcctttattactggtgtcttaaaacaatattattactaagtata
GCA A	ATG M	sag ,	AAT N	TTA L	taad	TTC	rtaco	TTG L	$_{\rm L}^{\rm TTG}$	AGA R	taac
TTA L	CAT	aato	$ ext{TTC}$	$_{\rm Y}^{\rm TAC}$	attt	AAG K	TG S	GGT G	TCA	AGA R	ttac
$\mathop{\mathrm{TTG}}_{L}$	AAA (aaat	AAA K	GCA A	actt	AAA.	AAA K	GAT D	CAG Q	CAT H	atta
ACA	ACG T	tgac	TCA	CAA	gagt	TGG W	GTC V	AGA R	TTT F	TTA L	caat
GAT D	$\frac{\text{CTG}}{\text{L}}$	tago	AAT N	GCA	G gt D	ATT.	GAA E	ATG M	CAA Q	TTT F	taaa
CTT L	GAG (E	ataa	CAC H	AGA R	ACG	AAA K	GCA A	GGA G	TAC Y	TTA L	gtct
TCT	GTA V	ıctga	ACC I	ATG M	ATA I	AGA R	TCT S	CTT	ATA I	GTG V	tggt
AGG R	TCT S	gtaa	ATT I	rGT	${ m TTC}$. GGA	TCC S	TGT C	CTA L	CAG Q	ttac
ATG M	ACA T	ıctgt	GAC	ATG M	ATG M	' ATT I	TTG L	TTT F	CAG Q	CGA R	ttta
AAC	TCT S	jtate	ATT I	TCT S	AGA R	' GTT	$^{\mathrm{TTC}}$	CTT L	GAA	TTG (atcc
GTG V	AAC N	AG R	TTT F	TAC Y	CAA	AAT N	CGT R	g G	TTC F	GTT V	atac
TCT S	TTT F	CTA L	GTA V	GGA G	CCC	TTC	AGG R	atca	TGC	CCA P	ttat
TTC F	TTA L	ATT I	CAA Q		ATT I	CTI	AGT	lacac		AGA R	ttta
GGT G	GCC A	AAA K	GCA A	AGG R	TTT F	ig AT	ACG I	attg	CAT H	CTA	tcaa
$ ext{TTC}$	GAA E	TAC Y	TTT F	$_{\rm Y}^{\rm TAT}$	ATA I	ctta	GGA TAT A	ıcaat	$_{\rm Y}^{\rm TAT}$	CCG P	attt
TTC	GAT D	TTT F	TCC S	ATA I	GAT	taac	GGA G	tcag	AAA K	AAG K	tgtc
CCA	ATT I	TTT F	GCA A	AAT N	AAG K	taat	TTA L	gagacttcagcaatattgacacatcag G	TTC F.	ATC	TAA *
ATG M	AAA K	TCT S	$_{\rm L}^{\rm CTT}$	TGC	ATG M	ıtcat	ATA I	tcga	TCT S	CTT L	
AGA R	CCT P	AAA K	AGC S	TGC	AGG R	aaagtcattaattaacottag AT	GAA ATA E I	ggtete	CCC	GAT D	GCT A
3901 799	3961 819	4021 839	4090 849	4150 869	4210 889	4275 904	4340 918	4402 936	4469 947	4529 967	4589 GCT GAT 987 A D

FIG. 15 (CONTINUED)

ļ. THE HAR SHALL

Atty. Docket No.: 015389-002630US
Applicant: Thomas R. Cech et al.
Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND
THERAPEUTIC METHODS
Sheet 19 of 34

19/34

(CONTINUED) FIG. 15

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 20 of 34

1	gcagcgctgc	gtcctgctgc	gcacgtggga	agccctggcc	ccggccaccc	ccgcgatgcc
C1	gagagetece	cactaccasa	ccatacactc -	cctactacac	agecaetace	gcgaggtgtt
121	accactaacc	acottcotoc	aacacctaaa	accccagggc	Lygeyyery	tycaycycyy
101	ggacccggcg	actttccaca	cactaataac	ccagtgcctg	atatacatac	cctgggacgc
101	acggccgccc	acceceges	cctccttcca	ccaggtgtcc	tocctoaago	agctggtggc
241	acggeegeee		~~~~~~~	cacasaasac	gractageet	tcaacttcac
301	ccgagtgctg	cagaggetgt	gegagegegg	cycyaagaac	3090099000	tacacaacta
361	gctgctggac	ggggcccgcg	ggggcccccc	cgaggccttc	accaccagcg	testestess
121	aataaaaaaa	accontracco	acccactccc	aaaaaacaaa	gcgcgggggc	Lyclyclycy
101	acacataaac	dacdacdtdc	togttcacct	actadcacac	Lgcgcgctcc	ctgtgttggt
E / 1	~~ataccaac	tacacctacc	addtatacaa	accaccacta	Lactagette	gegeegeeae
601	L	CCCCCCCCCCC	acactaataa	accccdaaqq	cattlegggat	gcgaacgggc
C C 1		agegteaggg	addccddddt.	cccctaaac	Cigicageee	cgggcgcgug
201	gaggcgcggg	agegeeaggg	accasatet	accattacce	aagaggccca	ggcgtggcgc
721	tgcccctgag	ggcagtgcca	geegaageee	acadaatcc	tagggggagg	coggcaggac
781	tgcccctgag	ecggagegga		estatesect	accadaccca	CCGAAGAAGC
841	gcgtggaccg	agtgaccgtg	gtttctgtgt	ggtgttactt	gecagaeeeg	tadaccacca
901	cacctctttg	gagggtgcgc	tctctggcac	gegeeaccec	cacccacccg	egggeegee
061	~~~~~~~~~	adcccccat	ccacatcgcg	accaccacqu	CCCLgggaca	cgccccgccc
1001		accasascas	accacetect	CLacticitica.	ggcgacaagg	agcageegeg
1001		ctactcacct	ctctgaggcc	cadcctdact	ggcgcccgga	ggcccgcga
4 -		atacattcca.	accetagat.	accadddaci	CCCCqcaggc	cgccccgccc
1201	~~~~~~~~~	tactoocaaa	racaacccct	deercradad	Cigcicggga	accacgogoa
1201	gtgcccctac	agatactac	traagargra	ctacccacta	caaactacaa	tcaccccagc
126T	agccggtgtc	ggggtgctcc	agacgca	gaactctata	acaacccca	aggaggagga
1321	agccggtgtc	tgtgcccggg	ayaaycccca	9990000000	accacccct	ggcaggtgta
1381	cacagacccc	cgtcgcctgg	Egcagetget	ccgccagcac	ageagetee	actecadaca
1441	cggcttcgtg	cgggcctgcc	tacaccaacr	ggtgcccca	ggcccccggg	aggetagget
1 5 0 1		cacttcctca	опаасассаа	daadttcatc	LCCCLGGGGG	agcacgccaa
1561		caddadctda	conogaagan	dadcdtdcdd	gactycyccc	ggccgcag
1621	~~~~~~~~~	attaactata	ttccaaccac	agaggaggg	Cigicgicgagg	agaccccggc
1 (01		cactaactaa	raaaratata	COECOECUAU	Ciquicagge	CCCCCCCC
1711	h	accacatttc	aaaadaacad	actettete	Lactygaaga	9-999-5
1001		accatteraa	rcadacadca	cttgaagagg	graderage	gggageegee
1001	Caageegeaa	atcaccagaa	atconggaage	caggeegge	ctactaacat	ccagactccg
1801	ggaagcagag	gccaggcagc	accyggaage	gattgtgaac	atggactacg	tcgtgggagc
1921	cttcatcccc	aageetgacg	ggctgcggcc	gactgtgaac	tegagggtga	aggcactgtt
1981	cagaacgttc	cgcagagaaa	agagggccga	gegeeceace	ctaagggcgc	aggcactgtt
2041	. cagcgtgctc	aactacgagc	agacacaaca	ecceggeete	ccgggcgccc	ctgtgctggg
2101	cotocaccat	atccacaggg	cctaacacac	cttcqtqcty	cgtgtgtggg	cccaggaccc
2161	accacctasa	ctgtactttg	tcaaggtgga	tqtqacgggc	gegtaegaea	CCaccccca
2221		acquaggtca	tegecageat	catcaaaccc	Cagaacacgu	actiguiguiguig
2201	+ caat a tacc	ataatccaaa	addccdccca	tagacacatc	cgcaaggccu	. ccaagagcca
2211	catatataca	ttgacagacc	ticcadeedta	catgcgacay	Licytyguu	accegeage
2401	~~~~~~~~~	ctaaaaaata	ccatcatcat	caaacaaaac	Locudoutya	acyayyccay
2401	. gaccagcetg	ttcgacgtct	tectacgett	catgtgccac	cacgccgtgc	gcatcagggg
2401	. caguggeete	- ctcgacgccc	aggggatccc	graggetee	atcctctcca	cgctgctctg
2521	. caagteetae	teggggggg	tagagaacaa	actatttaca	gggattcgg	gggacgggct
2581	. cagcctgtgc	Lacygogaca	cygagaacac	catascsct	cacctcaccc	acgcgaaaac
2641	. gctcctgcgt	trggrggarg	acception	. ggtgacacct	tacataataa	acttgggaa
2701	. cttcctcagg	accetggtee	gaggtgtccc	cgagtatggt	cacacacat	acttgcggaa
2761	L gacagtggtg	aacttccctg	tagaagacga	ggeeerggg	. ggcacggccc	ttgttcagat
2821	L gccggcccac	ggcctattcc:	cctggtgcgg	l ccracracra	gatacccgg	ccctggaggt
2001	acadadcdac	· tactccadct	atocccooac	: ctccatcaga	godagicic	Coccaace
20/1	caacttcaao	r actaggagga	acatocotco	r caaactcttt	: ggggtctty	gyctyaagty
2001	Lesesacete	, tttctaaatt	tacaaataaa	cadcctccad	acggugugu	CCaacaccca
2061	l concetecto	ctactacaaa	catacagatt	: tcacacatat	. gtgctgcay	LUCCALLUCA
2121	l toagcaagtt	tagaagaacc	ccacatttt	cctacacata	: attitude	a cygocococo
2101	l ctagtaaget	. cggaagaaca	ccaagaacg	agggatgtcc	r ctagagacca	a agggegeege
3183	l etgetactec	acccigaaag	ccaagaacg	, actatacca	caagcattco	tgctcaagct
3241	l cggccctctg	ceceegagg	ccgtgcagtg	geegegeede	ctcaggacaca	CCCAGACGCA
3301	L gactcgacac	: cgtgtcacct	acgugedaci	. cccggggcc		g cccagacgca
3361	l gctgagtcgg	g aagctcccgg	ggacgacgct	. gaccgccct	gaggeegeag	g ccaacccggc
3423	l actgccctca	ı gacttcaaga	ccatcctgga	ı ctgatggcca	cccgcccac	gccaggccga
3/101	l caccacacac	· caggaggggt	atcacacca	r gctctacgt	ccagggagg;	aggggcggcc
25/1	1 0202000	, cccacaccac	: taggagtete	r addcctdadi	gagtgtttg:	g ccgaggeetg
360	1 catatecaaa	tgaaggetga	i atateeaaet	: gaggcctgag	g cgagtgtcc	a gccaagggcc
266	1 ~~~tatacac	, cacacctgcc	· otetteaeti	. ccccacagg	: tagcactcg	g ctccaccca
270	yayiyiccay	, tacaccegce	adadcccaa.	ttccactcc	cacatagga	a tagtccatcc
3/4.	gggccagett		. ggagcccgg	- accetectt	cottocac	c cccaccatcc
3/8	ı ccagattcgo	cartgiteac	, coologood	- gccccccc	ttaaaataa	c caaaggtgtg
384	ı aggrggagac	cctgagaagg	accergggag			c caaaggtgtg
390	l ccctgtacac	c aggcgaggac	cctgcacct	gacggggg	t carttter	c aaattggggg
396	1 gaggtgctgt	t gggagtaaaa	tactgaata	L acgageeee	L cayttinga	u addad

Atty. Docket No.: 015389-002630US
Applicant: Thomas R. Cech et al.
Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND
THERAPEUTIC METHODS
Sheet 21 of 34

21/34

MPRAPRCRAVRSLLRSHYREVLPLATFVRRLGPQGWRLVQRGDP AAFRALVAQCLVCVPWDARPPPAAPSFRQVSCLKELVARVLQRL CERGAKNVLAFGFALLDGARGGPPEAFTTSVRSYLPNTVTDALR GSGAWGLLLRRVGDDVLVHLLARCALFVLVAPSCAYQVCGPPLY QLGAATQARPPPHASGPRRRLGCERAWNHSVREAGVPLGLPAPG ARRRGGSASRSLPLPKRPRRGAAPEPERTPVGQGSWAHPGRTRG PSDRGFCVVSPARPAEEATSLEGALSGTRHSHPSVGRQHHAGPP STSRPPRPWDTPCPPVYAETKHFLYSSGDKEQLRPSFLLSSLRP SLTGARRLVETIFLGSRPWMPGTPRRLPRLPQRYWQMRPLFLEL LGNHAQCPYGVLLKTHCPLRAAVTPAAGVCAREKPQGSVAAPEE EDTDPRRLVQLLRQHSSPWQVYGFVRACLRRLVPPGLWGSRHNE RRFLRNTKKFISLGKHAKLSLQELTWKMSVRDCAWLRRSPGVGC VPAAEHRLREEILAKFLHWLMSVYVVELLRSFFYVTETTFQKNR LFFYRKSVWSKLQSIGIRQHLKRVQLRELSEAEVRQHREARPAL LTSRLRFIPKPDGLRPIVNMDYVVGARTFRREKRAERLTSRVKA LFSVLNYERARRPGLLGASVLGLDDIHRAWRTFVLRVRAQDPPP ELYFVKVDVTGAYDTIPQDRLTEVIASIIKPQNTYCVRRYAVVQ KAAHGHVRKAFKSHVSTLTDLQPYMRQFVAHLQETSPLRDAVVI EQSSSLNEASSGLFDVFLRFMCHHAVRIRGKSYVQCQGIPQGSI LSTLLCSLCYGDMENKLFAGIRRDGLLLRLVDDFLLVTPHLTHA KTFLRTLVRGVPEYGCVVNLRKTVVNFPVEDEALGGTAFVQMPA HGLFPWCGLLLDTRTLEVQSDYSSYARTSIRASLTFNRGFKAGR NMRRKLFGVLRLKCHSLFLDLQVNSLQTVCTNIYKILLLQAYRF HACVLQLPFHQQVWKNPTFFLRVISDTASLCYSILKAKNAGMSL GAKGAAGPLPSEAVQWLCHQAFLLKLTRHRVTYVPLLGSLRTAQ TOLSRKLPGTTLTALEAAANPALPSDFKTILD

FIG. 17

TTATGTCACGGAGACCACGTTTCAAAAGAACAGGCTCTTTTTCTACCGGAAGAGTGTCTG GAGCAAGTTGCAAAGCATTGGAATCAGACAGCACTTGAAGAGGGTGCAGCTGCGGGAGCT CCGCTTCATCCCCAAGCCTGACGGGCTGCGGCCGATTGTGAACATGGACTACGTCGTGGG AGCCAGAACGTTCCGCAGAGAAAAGAGGGCCGAGCGTCTCACCTCGAGGGTGAAGGCACT GTTCAGCGTGCTCAACTACGAGCGGGCGCGCGCCCCGGCCTCCTGGGCGCCTCTGTGCT GGGCCTGGACGATATCCACAGGGCCTGGCGCACCTTCGTGCTGCGTGTGCGGGCCCAGGA CCCGCCGCCTGAGCTGTACTTTGTCAAGGTGGATGTGACGGGCGCGTACGACACCATCCC CCAGGACAGGCTCACGGAGGTCATCGCCAGCATCATCAAACCCCAGAACACGTACTGCGT GCGTCGGTATGCCGTGGTCCAGAAGGCCGCCCATGGGCACGTCCGCAAGGCCTTCAAGAG CCACGTCCTACGTCCAGTGCCAGGGGATCCCGCAGGGCTCCATCCTCTCCACGCTGCTCT GCAGCCTGTGCTACGGCGACATGGAGAACAAGCTGTTTGCGGGGGATTCGGCGGGACGGGC TGCTCCTGCGTTTGGTGGATGATTTCTTGTTGGTGACACCTCACCTCACCCACGCGAAAA CCTTCCTCAGGACCCTGGTCCGAGGTGTCCCTGAGTATGGCTGCGTGGTGAACTTGCGGA AGACAGTGGTGAACTTCCCTGTAGAAGACGAGGCCCTGGGTGGCACGGCTTTTGTTCAGA TGCCGGCCCACGGCCTATTCCCCTGGTGCGGCCTGCTGCTGGATACCCGGACCCTGGAGG TGCAGAGCGACTACTCCAGCTATGCCCGGACCTCCATCAGAGCCAGTCTCACCTTCAACC GCGGCTTCAAGGCTGGGAGGAACATGCGTCGCAAACTCTTTGGGGTCTTGCGGCTGAAGT GTCACAGCCTGTTTCTGGATTTGCAGGTGAACAGCCTCCAGACGGTGTGCACCAACATCT ACAAGATCCTCCTGCTGCAGGCGTACAGGTTTCACGCATGTGTGCTGCAGCTCCCATTTC ATCAGCAAGTTTGGAAGAACCCCACATTTTTCCTGCGCGTCATCTCTGACACGGCCTCCC TCTGCTACTCCATCCTGAAAGCCAAGAACGCAGGGATGTCGCTGGGGGCCAAGGGCGCCG CCGGCC7TCTGCCCTCCGAGGCCGTGCAGTGGCTGTGCCACCAAGCATTCCTGCTCAAGC TGACTCGACACCGTGTCACCTACGTGCCACTCCTGGGGTCACTCAGGACAGCCCAGACGC AGCTGAGTCGGAAGCTCCCGGGGACGACGCTGACTGCCCTGGAGGCCGCAGCCAACCCGG CACTGCCCTCAGACTTCAAGACCATCCTGGACTGATGGCCACCCGCCCACAGCCAGGCCG GCATGTCCGGCTGAAGGCTGAGTGTCCGGCTGAGGCCTGAGCGAGTGTCCAGCCAAGGGC TGAGTGTCCAGCACACCTGCCGTCTTCACTTCCCCACAGGCTGGCGCTCGGCTCCACCCC AGGGCCAGCTTTTCCTCACCAGGAGCCCGGCTTCCACTCCCCACATAGGAATAGTCCATC CCCAGATTCGCCATTGTTCACCCCTCGCCCTGCCCTCCTTTGCCTTCCACCCCCACCATC CAGGTGGAGACCCTGAGAAGGACCCTGGGAGCTCTGGGAATTTGGAGTGACCAAAGGTGT GCCCTGTACACAGGCGAGGACCCTGCACCTGGATGGGGGTCCCTGTGGGTCAAATTGGGG AAAAAAAAAAAAAA

Atty. Docket No.: 015389-002630US
Applicant: Thomas R. Cech et al.
Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND
THERAPEUTIC METHODS
Sheet 22 of 34

22/34

MetSerValTyrValValGluLeuLeuArgSerPhePhe TyrValThrGluThrThrPheGlnLysAsnArgLeuPhe PheTyrArgLysSerValTrpSerLysLeuGlnSerIle GlyIleArgGlnHisLeuLysArgValGlnLeuArgGlu LeuSerGluAlaGluValArgGlnHisArgGluAlaArg ProAlaLeuLeuThrSerArgLeuArgPheIleProLys ProAspGlyLeuArgProIleValAsnMetAspTyrVal ValGlyAlaArgThrPheArgArgGluLysArgAlaGlu ArgLeuThrSerArgValLysAlaLeuPheSerValLeu AsnTyrGluArgAlaArgArgProGlyLeuLeuGlyAla SerValLeuGlyLeuAspAspIleHisArgAlaTrpArg ThrPheValLeuArgValArgAlaGlnAspProProPro GluLeuTyrPheValLysValAspValThrGlyAlaTyr AspThrIleProGlnAspArgLeuThrGluValIleAla SerIleIleLysProGlnAsnThrTyrCysValArgArg TyrAlaValValGlnLysAlaAlaHisGlyHisValArg LysAlaPheLysSerHisValLeuArgProValProGly AspProAlaGlyLeuHisProLeuHisAlaAlaLeuGln ProValLeuArgArgHisGlyGluGlnAlaValCysGly AspSerAlaGlyArgAlaAlaProAlaPheGlyGly

CCNC	י רכרייי	יכרפיי	ירכייני	· ጉጥርር	CAC	'GTGG	GAAG	CCCI	GGCC	:ccgc	CCAC	cccc		1 met ATG
GCAG	,	.GCG1		,0100										
pro CCG	arg CGC	ala GCT	pro CCC	arg CGC	cys TGC	arg CGA	ala GCC	10 val GTG	arg CGC	ser TCC	leu CTG	leu CTG	arg CGC	ser AGC
his CAC	tyr TAC	arg CGC	20 glu GAG	val GTG	leu CTG	pro CCG	leu CTG	ala GCC	thr ACG	phe TTC	val GTG	arg CGG	30 arg CGC	leu CTG
gly GGG	pro CCC	gln CAG	gly GGC	trp TGG	arg CGG	leu CTG	val GTG	40 gln CAG	arg CGC	gly GGG	asp GAC	pro CCG	ala GCG	ala GCT
phe TTC	arg CGC	ala GCG	50 leu CTG	val GTG	ala GCC	gln CAG	cys TGC	leu CTG	val GTG	cys TGC	val GTG	pro CCC	60 trp TGG	asp GAC
ala GCA	arg CGG	pro CCG	pro CCC	pro CCC	ala GCC	ala GCC	pro CCC	70 ser TCC	phe TTC	arg CGC	gln CAG	val GTG	ser TCC	cys TGC
leu CTG	lys AAG	glu GAG	80 leu CTG	val GTG	ala GCC	arg CGA	val GTG	leu CTG	gln CAG	arg AGG	leu CTG	cys TGC	90 glu GAG	arg CGC
gly GGC	ala GCG	lys AAG	asn AAC	val GTG	leu CTG	ala GCC	phe TTC	100 gly GGC	phe TTC	ala GCG	leu CTG	leu CTG	asp GAC	gly GGG
ala GCC	arg CGC	gly GGG	110 gly GGC	pro CCC	pro CCC	glu GAG	ala GCC	phe TTC	thr ACC	thr ACC	ser AGC	val GTG	120 arg CGC	ser AGC

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 23 of 34

23/34

				•				120						
tyr TAC	leu CTG	pro CCC	asn AAC	thr ACG	val GTG	thr ACC	asp GAC	130 ala GCA	leu CTG	arg CGG	gly GGG	ser AGC	gly GGG	ala GCG
trp TGG	gly GGG	leu CTG	140 leu CTG	leu CTG	arg CGC	arg CGC	val GTG	gly GGC	asp GAC	asp GAC	val GTG	leu CTG	150 val GTT	his CAC
leu CTG	leu CTG	ala GCA	arg CGC	cys TGC	ala GCG	leu CTC	phe TTT	160 val GTG	leu CTG	val GTG	ala GCT	pro CCC	ser AGC	cys TGC
ala GCC	tyr TAC	gln CAG	170 val GTG	cys TGC	gly GGG	pro CCG	pro CCG	leu CTG	tyr TAC	gln CAG	leu CTC	gly GGC	180 ala GCT	ala GCC
thr ACT	gln CAG	ala GCC	arg CGG	pro CCC	pro CCG	pro CCA	his CAC	190 ala GCT	ser AGT	gly GGA	pro CCC	arg CGA	arg AGG	arg CGT
leu CTG	_gly _GGA	CYS TGC	200 glu GAA	arg CGG	ala GCC	trp TGG	asn AAC	his CAT	ser AGC	val GTC	arg AGG	glu GAG	210 ala GCC	gly GGG
val GTC	pro	leu CTG	gly GGC	leu CTG	pro CCA	ala GCC	pro CCG	220 gly GGT	ala GCG	arg AGG	arg AGG	arg CGC	gly GGG	gly GGC
ser AGT	ala GCC	a ser C AGO	230 arg	CAT	leu CTG	pro CCG	leu TTG	pro	lys AAG	arg AGG	pro	arg AGG	240 arg CGT	gly GGC
ala GCT	ala GCC	a pro	glu GAG	pro	glu GAG	arg	thr ACG	250 pro	val	gly	gln CAG	gly GGG	ser TCC	trp TGG
ala GCC	a his	s pro	260 gly GGC	, arc	thr ACG	arg GCGT	gly GGA	pro	ser AGT	asr GAC	arg CGT	gly GGT	270 phe TTC	cys TGT
va. GT0	l vai	l se G TC	r pro	o ala	a arg	pro	ala C GCC	280 a glu C GA <i>I</i>	ı glı	ı ala	thi C ACC	ser CTC	r leu r rro	glu GAG
al.	ادی	ale:	290) c alv	z thi	r arc	r his	s sei	c his	s pro	se:	r val	300 L gly	
gl: CA	n hi G CA	s hi C CA	s ala	a gly	y pro	pro C CC	o se: A TC	310 r thi	r se	r arg	g pro	o pro	o arg A CG:	g pro
tr TG	p as G GA	p th C AC	32° r pro G CC'	a av	s pro	o pro	o va G GT	l ty: G TA	r al C GC	a gl	u th	r ly C AA	330 s his G CA	o s phe C TTC

FIG. 20 (CONTINUED)

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 24 of 34

24/34

leu CTC	tyr TAC	ser TCC	ser TCA	gly GGC	asp GAC	lys AAG	alu	40 gln CAG	leu CTG	arg CGG	pro CCC	ser : TCC	phe TTC	leu CTA
leu CTC	ser AGC	ser TCT	350 leu CTG	arg AGG	pro CCC	ser AGC	leu CTG	thr ACT	gly GGC	ala GCT	arg CGG	arg	360 leu CTC	val GTG
glu GAG	thr ACC	ile ATC	phe TTT	leu CTG	gly GGT	ser TCC	arg AGG	370 pro CCC	trp TGG	met ATG	pro CCA	gly GGG	thr ACT	pro CCC
arg CGC	arg AGG	leu TTG	380 pro CCC	arg CGC	leu CTG	pro CCC	gln CAG	arg CGC	tyr TAC	trp TGG	gln CAA	met ATG	390 arg CGG	pro CCC
leu CTG	phe TTT	leu CTG	glu GAG	leu CTG	leu CTT	gly GGG	asn AAC	400 his CAC	ala GCG	gln CAG	cys TGC	pro CCC	tyr TAC	gly GGG
val GTG	_leu CTC	leu CTC	410 lys AAG	thr ACG	his CAC	cys TGC	pro CCG	leu CTG	arg CGA	ala GCT	ala GCG	val GTC	420 thr ACC	pro CCA
ala GCA	ala GCC	gly GGT	val GTC	cys TGT	ala GCC	arg CGG	glu GAG	430 lys AAG	pro	gln CAG	gly GGC	ser TCT	GIG	ala GCG
ala GCC	pro	glu GAG	440 glu GAG	glu GAG	asp GAC	thr ACA	asp GAC	pro	arg CGT	arg CGC	leu CTG	val GTG	450 gln CAG	leu CTG
leu CTC	arg	gln CAG	his CAC	ser AGC	ser	pro	trp TGG	460 gln CAG	val	tyr TAC	gly	phe TTC	val GTG	arg CGG
ala GCC	cys	leu CTG	470 arg CGC	aro	leu CTG	val GTG	pro	pro	gly GGC	leu CTC	trp TGG	gly	480 ser	arg AGG
his CAC	asr C AAC	n glu C GAA	arg A CGC	r arg	phe	lev CTC	arg AGC	490 g asr G AAC	ı thi	lys AAC	lys AAG	phe TTC	ile : ATC	ser TCC
let CTC	ı gly	y lys 3 AAC	500 his CAT		lys AAC	leu CTC	ı sei C TCC	c lev	ı glı G CA(n glu G GAC	leu CTG	thr ACG	510 trp TGC	lys AAG
met ATC	t sei G AG	r val	l arg	g as <u>r</u> G GAC	o cys	s ala	a tri	520 p len G CTO	ıar	g arg	g ser G AGO	pro	o gly A GGO	val GTT
gly GG	y cy: C TG	s vai	530 l pro r cco	n ala	a ala C GCZ	a gli A GA(u hi: G CA	s arg	g le T CT	u arg G CG	g glu r GAC	ı glı G GA(540 1 ile 3 ATO) e leu C CTG

FIG. 20 (CONTINUED)

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 25 of 34

25/34

								5	550						
ć	ala GCC	lys AAG	phe TTC	leu CTG	his CAC	trp TGG	leu CTG	met ATG	ser AGT	val GTG	tyr TAC	val GTC	val GTC	glu GAG	leu CTG
					phe TTT										
i	arg AGG	leu CTC	phe TTT	phe TTC	tyr TAC	arg CGG	lys AAG	ser AGT	580 val GTC	trp TGG	ser AGC	lys AAG	leu TTG	gln CAA 600	ser AGC
	ile ATT	gly GGA	ile ATC	arg	gln CAG	his CAC	leu TTG	lys AAG	arg AGG	val GTG	gln CAG	leu CTG	arg ÇGG	glu	leu CTG
	ser TCG	glu GAA	ala GCA	glu GAG	val GTC	arg AGG	gln CAG	his CAT	610 arg CGG	glu GAA	ala GCC	arg AGG	pro CCC	ala GCC	leu CTG
	leu CTG	thr _ACG	ser TCC	620 arg AGA	leu CTC	arg CGC	phe TTC	ile ATC	pro CCC	lys AAG	pro CCT	asp GAC	gly GGG	630 leu CTG	arg CGG
	pro CCG	ile ATT	val GTG	asn AAC	met ATG	asp GAC	tyr TAC	val GTC	640 val GTG	gly GGA	ala GCC	arg AGA	thr ACG	phe TTC	arg CGC
	arg AGA	glu GAA	lys AAG	650 arg AGG	ala GCC	glu GAG	arg CGT	leu CTC	thr ACC	ser TCG	arg AGG	val GTG	lys AAG	660 ala GCA	leu CTG
- 1	phe TTC	ser AGC	val GTG	leu CTC	asn AAC	tyr TAC	glu GAG	arg CGG	670 ala GCG	arg CGG	arg CGC	pro CCC	gly GGC	leu CTC	leu CTG
	ggc gly	ala GCC	ser TCT	680 val GTG	leu CTG	GGC Gly	leu CTG	asp GAC	asp GAT	ile ATC	his CAC	arg AGG	ala GCC	690 trp TGG	arg CGC
	thr ACC	phe TTC	val GTG	leu CTG	arg CGT	val GTG	arg CGG	ala GCC	700 gln CAG	asp GAC	pro CCG	pro CCG	pro CCT	glu GAG	leu CTG
	tyr TAC	phe TTT	val GTC	710 lys AAG	val GTG	asp GAT	val GTG	thr ACG	gly	ala GCG	tyr TAC	asp GAC	thr ACC	720 ile ATC	pro CCC
	gln CAG	asp GAC	arg AGG	leu CTC	thr ACG	glu GAG	val GTC	ile ATC	730 ala GCC	ser AGC	ile ATC	ile ATC	lys AAA	pro CCC	gln CAG
	asn AAC	thr ACG	tyr TAC	740 cys TGC	val GTG	arg CGT	arg CGG	tyr TAT	ala GCC	val GTG	val GTC	gln CAG	lys AAG	750 ala GCC	ala GCC

FIG. 20 (CONTINUED) Atty. Docket No.: 015389-002630US
Applicant: Thomas R. Cech et al.
Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND
THERAPEUTIC METHODS
Sheet 26 of 34

26/34

760 his gly his val arg lys ala phe lys ser his val leu arg pro CAT GGG CAC GTC CGC AAG GCC TTC AAG AGC CAC GTC CTA CGT CCA 780 770 val pro gly asp pro ala gly leu his pro leu his ala ala leu GTG CCA GGG GAT CCC GCA GGG CTC CAT CCT CAC GCT GCT CTG 790 gln pro val leu arg arg his gly glu gln ala val cys gly asp CAG CCT GTG CTA CGG CGA CAT GGA GAA CAA GCT GTT TGC GGG GAT 807 ser ala gly arg ala ala pro ala phe gly gly OP TCG-GCG-GGA CGG GCT GCT CCT GCG TTT GGT GGA TGA TTTCTTGTTGGT GACACCTCACCTCACCCACGCGAAAACCTTCCTCAGGACCCTGGTCCGAGGTGTCCCTGA GTATGGCTGCGTGAACTTGCGGAAGACAGTGGTGAACTTCCCTGTAGAAGACGAGGC CCTGGGTGGCACGGCTTTTGTTCAGATGCCGGCCCACGGCCTATTCCCCTGGTGCGGCCT GCTGCTGGATACCCGGACCCTGGAGGTGCAGAGCGACTACTCCAGCTATGCCCGGACCTC CATCAGAGCCAGTCTCACCTTCAACCGCGGCTTCAAGGCTGGGAGGAACATGCGTCGCAA ACTCTTTGGGGTCTTGCGGCTGAAGTGTCACAGCCTGTTTCTGGATTTGCAGGTGAACAG CCTCCAGACGGTGTGCACCAACATCTACAAGATCCTCCTGCTGCAGGCGTACAGGTTTCA CGCATGTGTGCTGCAGCTCCCATTTCATCAGCAAGTTTGGAAGAACCCCACATTTTTCCT GCGCGTCATCTCTGACACGGCCTCCCTCTGCTACTCCATCCTGAAAGCCAAGAACGCAGG GATGTCGCTGGGGGCCAAGGGCGCCGCCGGCCCTCTGCCCTCCGAGGCCGTGCAGTGGCT GTGCCACCAAGCATTCCTGCTCAAGCTGACTCGACACCGTGTCACCTACGTGCCACTCCT GGGGTCACTCAGGACAGCCCAGACGCAGCTGAGTCGGAAGCTCCCGGGGACGACGCTGAC TGCCCTGGAGGCCGCAGCCAACCCGGCACTGCCCTCAGACTTCAAGACCATCCTGGACTG CTACGTCCCAGGGAGGGAGGGCGGCCCACACCCAGGCCCGCACCGCTGGGAGTCTGAGG CCTGAGTGAGTGTTTGGCCGAGGCCTGCATGTCCGGCTGAAGGCTGAGTGTCCGGCTGAG GCCTGAGCGAGTGTCCAGCCAAGGGCTGAGTGTCCAGCACACCTGCCGTCTTCACTTCCC CACAGGCTGGCGCTCGGCTCCACCCCAGGGCCAGCTTTTCCTCACCAGGAGCCCGGCTTC CACTCCCCACATAGGAATAGTCCATCCCCAGATTCGCCATTGTTCACCCCTCGCCCTGCC CTCCTTTGCCTTCCACCCCACCATCCAGGTGGAGACCCTGAGAAGGACCCTGGGAGCTC TGGGAATTTGGAGTGACCAAAGGTGTGCCCTGTACACAGGCGAGGACCCTGCACCTGGAT GGGGGTCCCTGTGGGTCAAATTGGGGGGGGGGTGCTGTGGGAGTAAAATACTGAATATATG

FIG. 20 (CONTINUED)

Atty. Docket No.: 015389-002630US
Applicant: Thomas R. Cech et al.
Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND
THERAPEUTIC METHODS
Sheet 27 of 34

27/34

3601	ATCGATTGGGCCCGAGATCTCGCGCGCGAGGCCTGCCATGGGACCCACTGCAGGGCAGC TAGCTAACCCGGGCTCTAGAGCGCGCGCTCCGGACGTACCCTGGGTGACGTCCCCGTCG ^
	3615 3636 BGL2 NCO1
3661	TGGGANGCTGCAGGCTTCAGGTCCCAGTGGGGTTGCCATCTGCCAGTAGAAACCTGATGT ACCCTNCGACGTCCGAAGTCCAGGGTCACCCCAACGGTAGACGGTCATCTTTGGACTACA
3721	AGAATCAGGGCGCGAGTGTGGACACTGTCCTGAATCTCAATGTCTCAGTGTGTGCTGAAA TCTTAGTCCCGCGCTCACACCTGTGACAGGACTTAGAGTTACAGAGTCACACACGACTTT
3781	CATGTAGAAATTAAAGTCCATCCCTCCTACTCTACTGGGATTGAGCCCCTTCCCTATCCC GTACATCTTTAATTTCAGGTAGGGAGGATGAGATGA
3841	CCCCCAGGGGCAGAGGAGTTCCTCTCACTCCTGTGGAGGAAGGA
3901	TTTCACTGCTGGTACTGAATCCACTGTTTCATTTGTTGGTTTGTTT

3961	AGCGGTTTCACTCTTGTTGCTCAGGCTGGANGGAGTGCAATGGCGCGATCTTGGCTTACT TCGCCAAAGTGAGAACAACGAGTCCGACCTNCCTCACGTTACCGCGCTAGAACCGAATGA
	ALU

4021	GCAGCCTCTGCCTCCCAGGTTCAAGTGATTCTCCTGCTTCCGCCTCCCATTTGGCTGGGA CGTCGGAGACGGAGGGTCCAAGTTCACTAAGAGGACGAAGGCGGAGGGTAAACCGACCCT

4081	
	AATG1CCG1GGCGG1GG1ACGGG1CGA11AAAAAACA1AAAAA1CA1W1W1GNCCCCAC
	A
4141	GGGGTGGGGTTCACATGTTGGCCAAGCTGGTCTCGAACTTCTGAACTCAGATGATCCANC CCCCACCCCAAGTGTACAACCGGTTCGACCAGAGCTTGAAGACTTGAGTCTACTAGGTNG
	LU
4201	TGCCTCTGCCTCCTAAAATTGCTGGGATTACAGGTGTNANCCACCATGCCCAACTCAAAA ACGGAGACGGAGGATTTAACGACCCTAATGTCCACANTNGGTGGTACGGGTTGAGTTTT
4261	TTTACTCTGTTTANAAACATCTGGGTCTAAGGTAGGAANCTCACCCCACTCAATTTTTGT AAATGAGACAAATNTTTGTAGACCCAGATTCCATCCTTNGAGTGGGGTGAGTTAAAAACA

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al. Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND THERAPEUTIC METHODS Sheet 28 of 34

28/34

4321	${\tt GGTGTTTTAAGCCAATNANAAAATTTTTTNATGTTGTTTNNNNNNNNNN$
4381	имимимимимимимимимимимимимимимимимимим
4441	имимимимимимимимимимимимимимимимимимим
4501	имимимимимимимимимимимимимимимимимимим
4561	имимимимимимимимимимимимимимимимимимим
4621	имимимимимимимимимимимимимимимимимимим
4681	иилимимимимимимимимимимимимимимимимимим
4741	имимимимимимимимимимимимимимимимимимим
4801	имимимимимимимимимимимимимимимимимимим
4861	ИМИМИМИМИМИМИМИМИМИМИМИМИМИМИМИМИМИМИМ
4921	имимимимимимимимимимимимимимимимимимим
4981	NIMININININININININININININININININININ
5041	NGCCANGRAGGGGCCAGGTTCCAANTTCCCAACCKTTTTWGGARGGACNGCCCCAGGG NCGGTNCYTCCCCGGTCCAAGGTTNAAGGGTTGGMAAAAWCCTYCCTGNCGGGGGTCCC
5101	GGGGATRAACAGANTNGGGGGKGGTWGGGTTNAKGGTGGGAACNCCTTNGCGCCTGGAG CCCCTAYTTGTCTNANCCCCCMCCAWCCCAANTMCCACCCTTGNGGAANCGSCGGACCTC
5161	AACGTGCAAAGAGGAAATGAAGGGCCTGKGTCAAGGAGCCCAAGTNGGCGGGGRAGTTTG TTGCACGTTTCTCCTTTACTTCCCGGACMCAGTTCCTCGGGTTCANCCGCCCCYTCAAAC
5221	CAGGGAGCACTCCGGGGAGGTCCSGCGTGCCCGTCCAAGGGAGCAATGCGTCCTTCGGGGTCCCTCCGTGAGGCCCCTCCAGGSCGCACGGGCAGGTTCCCTCGTTACGCAGGAAGCCC
5281	TTCGTCCCCAWGCCGCGTCTACGCGCCTYCCGTCCTCCCCTTCACGTTCCGGCATTCGTGAAGCAGGGGTWCGGCGCAGATGCGCGGARGGCAGGAGGGGAAGTGCAAGGCCGTAAGCAC
5341	GTGCCCGGAGCCCGACGCCCGCGTCCGGACCTGGAGGCAGCCCTGGGTCTCCGGATCAGCACGGGCCTCGGGCTCCGGGGCCTAGTC
5401	GCCAGCGGCCAAAGGGTCGCCGCACGCACCTGTTCCCAGGGCCTCCACATCATGGCCCCTCGGTCGCCGGGTTTCCCAGCGGCGTGCGT
	EIC 01

FIG. 21 (CONTINUED)

Atty. Docket No.: 015389-002630US Applicant: Thomas R. Cech et al.

Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND

THERAPEUTIC METHODS Sheet 29 of 34

29/34

5461 CCCTCGGGTTACCCCACAGCCTAGGCCGGATTCGACCTCTCTCCGCTGGGGCCCTCGCCT GGGAGCCCAATGGGGTGTCGGATCCGGCCTAAGCTGGAGAGAGGCGACCCCGGGAGCGGA

Sp1 ****

- 5521 GGCGTCCCTGCACCCTGGGAGCGCGAGCGCGCGCGGGGGGAAGCGCGGCCCATACCC CCGCAGGGACGTGGGACCCTCGCGCTCGCCGCGCCCCCTTCGCGCCGGGTATGGG
- 5581 CCGGGTCCGCCCGGAAGCAGCTGCGCTGTCGGGGCCAGGCCGGGCTCCCAGTGGATTCGC GGCCCAGGCGGGCCTTCGTCGACGCGACAGCCCCGGTCCGGCCCGAGGGTCACCTAAGCG

Topo_II_cleavage_site *****

5641 GGGCACAGACGCCCAGGACCGCGCTTCCCACGTGGCGGAAGGACTGGGGACCCGGGCACC CCCGTGTCTGCGGGTCCTGGCGCGAAGGGTGCACCGCCTTCCTGACCCCTGGGCCCGTGG

E2F *****

GCAGGACGGGGAAGTGGAAGGTCGAGGCGAAGAAGGCGCGCCTGGGCCGGGGCAGGGCTT

Sp1

=======

NFkB 2F *****

h ******

5821 CGCGGCCCCCCCTCTCCTTCGCGCGCGAGTTTCAGGCAGCGCTGCGTCCTGCTGCGCA GCGCCGGGGCGGAGAGGAAGCGCCGCGCTCAAAGTCCGTCGCGACGCAGGACGACGCGT

> 5860 ECO47III

5875 FSP1

TRT5' *******

- 5881 CGTGGGAAGCCCTGGCCCCGGCCACCCCGCGATGCCGCGCGCTCCCCGCTGCCGAGCCG GCACCCTTCGGGACCGGGGCCGTGGGGGCGCTACGGCGCGCGAGGGGCGACGGCTCGGC
- 5941 TGCGCTCCCTGCTGCGCAGCCACTACCGCGAGGTGCTGCCGCTGGCCACGTTCGTGCGGC ACGCGAGGGACGACGCGTCGGTGATGGCGCTCCACGACGGCGACCGGTGCAAGCACGCCG

5953

FSP1

- 6001 GCCTGGGGCCCCAGGGCTGGCGGCTGCTGCAGCGCGGGACCCGGCGGCTTTCCGCGCGC CGGACCCCGGGGTCCCGACCGCCGACCACGTCGCGCCCTGGGCCGCCGAAAGGCGCGCG

NFkB

========

FIG. 21 (CONTINUED) Atty. Docket No.: 015389-002630US
Applicant: Thomas R. Cech et al.
Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND
THERAPEUTIC METHODS
Sheet 30 of 34

	30/34
6121	**************************************
	Topo_II_cleavage_s :::::::::::: NFkB ========
	<pre>Intron1 ************************************</pre>
6181	GGAACCAGCGACATGCGGAGAGCAGCGCAGGCGACTCAGGGCGCTTCCCCCGCAGGTGTC CCTTGGTCGCTGTACGCCTCTCGTCGCGTCCGCTGAGTCCCGCGAAGGGGGCGTCCACAG
	ite
	<u> </u>
6241	CTGCCTGAAGGAGCTGGTGGCCCGAGTGCTGCAGAGGCTGTGCGAGCGCGCGAAGAA GACGGACTTCCTCGACCACCGGGCTCACGACGTCTCCGACACGCTCGCGCCGCGCTTCTT
6301	CGTGCTGGCCTTCGGCTTCGCGCTGCTGGACGGGGCCCCGGGGGGCCCCCCGAGGCCTTGCACGACCGGAAGCCGAAGCCGACGACCTGCCCCGGGGCGCCCCCGGGGGGGCCTCCGGAA
6361	CACCACCAGCGTGCGCAGCTACCTGCCCAACACGGTGACCGACGCACTGCGGGGGAGCGG GTGGTGGTCGCACGCGTCGATGGACGGGTTGTGCCACTGGCTGACGCCCCCTCGCC
	6372 FSP1
6421	GGCGTGGGGGCTGCTGCGCCGCGTGGGCGACGACGTGCTGGTTCACCTGCTGGCACG CCGCACCCCGACGACGACGCGCGCGCACCCGCTGCTGCACGACCAAGTGGACGACCGTGC
6481	CTGCGCGCTCTTTGTGCTGGTGGCTCCCAGCTGCGCCTACCAGGTGTGCGGGCCGCCGCTGACGCGCGAGAAACACGACCACCGAGGGTCGACGCGGATGGTCCACACGCCCGGCGGCGA
6541	GTACCAGCTCGGCGCTGCCACTCAGGCCCGGCCCCCCCCC
6601	GCGTCTGGGATGCGAACGGGCCTGGAACCATAGCGTCAGGGAGGCCGGGGTCCCCTGGG CGCAGACCCTACGCTTGCCCGGACCTTGGTATCGCAGTCCCTCCGGCCCCAGGGGGACCC
6661	CCTGCCAGCCCGGGTGCGAGGAGGCGCGGGGGCAGTGCCAGCCGAAGTCTGCCGTTGCCGGACGGTCGGGGCCCACGCTCCTCCGCGCCCCCGTCACGGTCGGCTTCAGACGGCAACGG
6721	CAAGAGGCCCAGGCGTGGCGCTGCCCCTGAGCCGGAGCGGACGCCCGTTGGGCAGGGGTCGTTCTCCGGGTCCGCACCGCGACGGGGACTCGGCCTGCCGGCAACCCGTCCCCAG
6781	CTGGGCCCACCCGGGCAGGACGCGTGGACCGAGTGACCGTGGTTTCTGTGTGGTGTCACCGACCG
6841	TGCCAGACCCGCCGAAGAAGCCACCTCTTTGGAGGGTGCGCTCTCTGGCACGCGCCACTC ACGGTCTGGGCGGCTTCTTCGGTGGAGAAACCTCCCACGCGAGAGACCGTGCGCGGTGAG
6901	CCACCCATCCGTGGGCCGCCAGCACCACGCGGGCCCCCCATCCACATCGCGGCCACCACG

FIG. 21 (CONTINUED)

GGTGGGTAGGCACCCGGCGGTCGTGGTGCGCCCGGGGGGTAGGTGTAGCGCCGGTGGTGC

Atty. Docket No.: 015389-002630US
Applicant: Thomas R. Cech et al.
Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND
THERAPEUTIC METHODS
Sheet 31 of 34

31/34

6961	TCCCTGGGACACGCCTTGTCCCCCGGTGTACGCCGAGACCAAGCACTTCCTCTACTCCTC AGGGACCCTGTGCGGAACAGGGGGCCACATGCGGCTCTGGTTCGTGAAGGAGATGAGGAG
7023	AGGCGACAAGGAGCAGCTGCGGCCCTCCTTCCTACTCAGCTCTCTGAGGCCCAGCCTGAC TCCGCTGTTCCTCGTCGACGCCGGGAGGAAGGATGAGTCGAGAGACTCCGGGTCGGACTG
708	TGGCGCTCGGAGGCTCGTGGAGACCATCTTTCTGGGTTCCAGGCCCTGGATGCCAGGGACACCGGGAGCCTCCGAGCACCTCTGGTAGAAAGACCCAAGGTCCGGGACCTACGGTCCCTG
714	TCCCCGCAGGTTGCCCCGCCTGCCCAGCGCTACTGGCAAATGCGGCCCCTGTTTCTGGA AGGGGCGTCCAACGGGGCGACGGGGTCGCGATGACCGTTTACGCCGGGGACAAAGACCT
	7167 ECO47III
720	I GCTGCTTGGGAACCACGCGCAGTGCCCCTACGGGGTGCTCCTCAAGACGCACTGCCCGCT CGACGAACCCTTGGTGCGCGTCACGGGGATGCCCCACGAGGAGTTCTGCGTGACGGCGA
726	1 GCGAGCTGCGGTCACCCCAGCAGCCGGTGTCTGTGCCCGGGAGAAGCCCCAGGGCTCTGT CGCTCGACGCCAGTGGGGTCGTCGGCCACAGACACGGGCCCTCTTCGGGGTCCCGAGACA
	1 GGCGGCCCCGAGGAGGAGGACACAGACCCCCGTCGCCTGGTGCAGCTGCTCCGCCAGCA
732	CCGCCGGGGCTCCTCCTCTGTGTCTGGGGGCAGCACACACA
	CCGCCGGGGGCTCCTCCTGTGTCTGGGGGCGCGGACCACGTCGACGAGGGGTCGT
738	1 CAGCAGCCCCTGGCAGGTGTACGGCTTCGTGCGGGCCTGCCT
744	1 AGGCCTCTGGGGCTCCAGGCACAACGAACGCCGCTTCCTCAGGAACACCAAGAAGTTCAT TCCGGAGACCCCGAGGTCCGTGTTGCTTGCGGCGAAGGAGTCCTTGTGGTTCTTCAAGTA
750	1 CTCCCTGGGGAAGCATGCCAAGCTCTCGCTGCAGGAGCTGACGTGGAAGATGAGCGTGCG GAGGGACCCCTTCGTACGGTTCGAGAGCGACGTCCTCGACTGCACCTTCTACTCGCACGC

756	1 GGACTGCGCTTGGCTGCGCAGGAGCCCAGGTGAGGAGGTGGTGGCCGTCGAGGGCCCAGG CCTGACGCGAACCGACGCGTCCTCGGGTCCACCACCACCGGCAGCTCCCGGGTCC
	7575 FSP1
	Intron2

762	1 CCCCAGAGCTGAATGCAGTAGGGGCTCAGAAAAGGGGGCAGGCA

769	31 GTCTCCATCGTCACGTGGCCACACGTGGCTTTTCGCTCAGGACGTCGAGTGGACACGGTG
700	CAGAGGTAGCACCCGTGTGCACCGAAAAGCGAGTCCTGCAGCTCACCTGTGCCAC
	**>
77	ATCGAGGTCGACTCTAGAGGATCCCCGGGTACCGAGCTCGAATTCGTAATCATGGTCATA TAGCTCCAGCTGAGATCTCCTAGGGGCCCCATGGCTCGAGCTTAAGCATTAGTACCAGTAT
	7747

FIG. 21 (CONTINUED)

SAL1

Α

off the first that the first care that

Ħ [] |-

ļ

<u>F</u>å

IJ N Atty. Docket No.: 015389-002630US
Applicant: Thomas R. Cech et al.
Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND
THERAPEUTIC METHODS
Sheet 32 of 34

trt1+

500 bp

32/34

7 8 9 1011 12 13 14 15 56 1 2 3 Introns - Original PCR Product ura4+ deletion ura4+ his3+ deletion his3+ HK Xc Н Хc Xc Xh ĸ Xb Xc D В trt1+ Tetrad 0 trt1+ trt1_ trt1+ trt1 1500 bp O 8 600 bp 500 bp 400 bp 0 300 bp **—**10 μm <u>trt1</u>-200 bp 100 bp 1 2 3 4 5 6 7 8 9 10 11 12 13 trt1+ trt1-

FIG. 22

Atty. Docket No.: 015389-002630US

Applicant: Thomas R. Cech et al.

Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND

THERAPEUTIC METHODS

Sheet 33 of 34

33/34

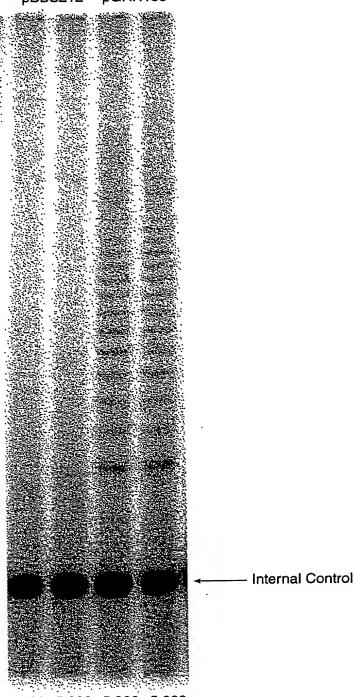
FIG. 23

TCTACCTTGACAGACCTCCAGCCGTACATGCGACAGTTCGTGGCTCACCTGCAGGAG ACCAGCCCGCTGAGGGATGCCGTCGTCATCGAGCAGAGCTCCTCCCTGAATGAGGCC AGCAGTGGCCTCTTCGACGTCTTCCTACGCTTCATGTGCCACCACGCCGTGCGCATC AGGGGCAAGTC

Atty. Docket No.: 015389-002630US
Applicant: Thomas R. Cech et al.
Title: HUMAN TELOMERASE CATALYTIC SUBUNIT: DIAGNOSTIC AND
THERAPEUTIC METHODS
Sheet 34 of 34

34/34

pBBS212 pGRN133



Approximate Cell No.

5,000 5,000 5,000 5,000